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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Paper No. 18

Application Number: 09/841,758
Filing Date: 4/24/2001
Appellant(s): BANDMAN ET AL

Susan Sather
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 8/12/2003 (paper no. 17).

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

Appellant's brief includes a statement that the claims stand or fall together.

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

5,194,596	***TISCHER ET AL***	***3-1993***
5,350,836	***KOPCHICK ET AL***	***9-1994***

Benjamin et al Development 1998; 128:1591-1598

Bork Trends in Genetics 1996;12:425-427

Bork Genome Research 2000;10:398-400

Bowie et al Science 1990;247:1306-1310

Burgess et al J. of Cell Biol. 1990;111:2129-2138

Brenner Trends in Genetics 1999;15:132-133

Doerks et al Trends in Genetics 1998;14:248-250

Lazar et al Molecular and Cellular Biology 1988;8:1247-1252

Massague Cell 1987;49:437-438

Pilbeam et al Bone 1993;14:717-720

Scott et al Nature Genetics 1999; 21:440-443

Skolnick et al Trends in Biotech. 2000;18:34-39

Smith et al Nature Biotechnology 1997;15:1222-1223

Vukicevic et al PNAS USA 1996; 93:9021-9026

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

35 U.S.C. 101 (Issue 1)

Claims 1-2, 13, and 14 are rejected under 35 USC 101. This rejection is set forth below.

Claims 1-2 and 13-14 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific asserted utility or a well established utility.

Claims are drawn to an amino acid sequence of SEQ ID NO:1, a naturally occurring amino acid sequence having at least 96% sequence identity to SEQ ID NO:1,

a biologically active fragment of SEQ ID No:1, an immunogenic fragment of SEQ ID No:1, and a composition comprising an amino acid sequence of SEQ ID NO:1 in a pharmaceutically acceptable excipient.

The disclosed utilities for a novel human selenium-binding protein (herein referred to as HSEBP) comprising the amino acid sequence of SEQ ID NO:1, or naturally-occurring amino acid sequences with at least 96% identity with SEQ ID NO:1 include diagnosis, prevention and treatment of chemically-induced damage, carcinogenesis, and cancer (specification, pp.1, 2, and 25). However, neither the specification nor any art of record teaches what HSEBP is, or what it does do. Furthermore, the specification does not disclose any amino acids which are 96% identical to that of SEQ ID No: 1. They do not teach a relationship to any specific diseases or establish any involvement in the etiology of any specific diseases. The asserted utilities for HSEBP, such as the production of and screening of antibodies and antagonists apply to many unrelated polypeptide structure sequences. Therefore, the asserted utilities are not considered "specific" utilities, i.e. they are not specific to HSEBP. Additional disclosed utilities for HSEBP include therapy and diagnosis of conditions and diseases characterized by the expression of HSEBP. The asserted utilities for HSEBP is based on the assertion that HSEBP (SEQ ID NO:1) has chemical and structural homology to selenium-binding proteins (specification, p.3 last line and p.16) and that in particular HSEBP and human fetal heart selenium-binding protein, mouse liver selenium binding protein, and mouse liver acetaminophen-binding protein, share 96%,86%, and 88% identity, respectively (specification pp. 12 lines 30-31).

However, it is clear that, although there is a 96%, 86%, and 88% identity between human fetal heart selenium-binding protein, mouse liver selenium binding protein, and mouse liver acetaminophen-binding protein and SEQ ID NO:1, there is a 4%, 14% , and 12% dissimilarity between SEQ ID NO:1 and the sequence of human fetal heart selenium-binding protein, mouse liver selenium binding protein, and mouse liver acetaminophen-binding protein, and the effects of these dissimilarities upon protein structure and function cannot be predicted. Bowie et al (Science, 1990, 257 : 1306-1310) teach that an amino acid sequence encodes a message that determine the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instruction of the genome and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex (col.1, p.1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitution can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col.2, p.1306). The sensitivity of proteins to alterations of even a single amino acid in a sequence are exemplified by Burgess et al (J of Cell Biol. 111:2129-2138, 1990) who teach that replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss

of heparin binding, receptor binding and biological activity of the protein and by Lazar et al (Molecular and Cellular Biology, 1988, 8:1247-1252) who teach that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. These references demonstrate that even a single amino acid substitution will often dramatically affect the biological activity and characteristics of a protein. Clearly, with 4%, 14%, and 12% dissimilarity to human fetal heart selenium-binding protein, mouse liver selenium binding protein, and mouse liver acetaminophen-binding protein, the function of the SEQ ID NO:1 polypeptide could not be predicted, based on sequence similarity with human fetal heart selenium-binding protein, mouse liver selenium binding protein, and mouse liver acetaminophen-binding protein, nor would it be expected to be the same as that of human fetal heart selenium-binding protein, mouse liver selenium binding protein, and mouse liver acetaminophen-binding protein. In addition, Bork (Genome Research, 2000,10:398-400) clearly teaches the pitfalls associated with comparative sequence analysis for predicting protein function because of the known error margins for high-throughput computational methods. Bork specifically teaches that computational sequence analysis is far from perfect, despite the fact that sequencing itself is highly automated and accurate (p. 398, col 1). One of the reasons for the inaccuracy is that the quality of data in public sequence databases is still insufficient. This is particularly true for data on protein function. Protein function is context dependent, and both molecular and cellular aspects have to be considered (p. 398, col 2). Conclusions from

the comparison analysis are often stretched with regard to protein products (p. 398, col 3). Furthermore, recent studies show that alternative splicing might affect more than 30% of human genes and the number of known post-translational modifications of gene products is increasing constantly so that complexity at protein level is enormous. Each of these modifications may change the function of respective gene products drastically (p. 399, col 1). Further, although gene annotation via sequence database searches is already a routine job, even here the error rate is considerable (p. 399, col 2). Most features predicted with an accuracy of greater than 70% are of structural nature and at best only indirectly imply a certain functionality (see legend for table 1, page 399). As more sequences are added and as errors accumulate and propagate it becomes more difficult to infer correct function from the many possibilities revealed by database search (p. 399para bridging cols 2 and 3). The reference finally cautions that although the current methods seem to capture important features and explain general trends, 30% of those feature are missing or predicted wrongly. This has to be kept in mind when processing the results further (p. 400, para bridging cols 1 and 2). Further, Scott et al (Nature Genetics, 1999, 21:440-443) teach that the gene causing Pendred syndrome encodes a putative transmembrane protein designated pendrin. Based on sequence similarity data, the authors postulated that the putative protein was deemed to be a member of sulfate transport proteins that included a 29% identity to rat sulfate-anion transporter, 32% similarity to human diastrophic dysplasia sulfate transporter, and 45% similarity to the human sulfate transporter 'downregulated in adenoma'. However, upon analyzing the expression and kinetics of the protein, the data revealed no evidence of

sulfate transport wherein results revealed that pendrin functioned as a transporter of chloride and iodide. Scott et al. suggest that these results underscore the importance of confirming the function of newly identified gene products even when the database searches reveal significant homology to proteins of known function (page 411, 1st column, 4th paragraph).

Clearly, given not only the teachings of Bowie et al, Scott et al, Lazar et al and Burgess et al but also the limitations and pitfalls of using computational sequence analysis and the unknown effects of alternative splicing, post translational modification and cellular context on protein function as taught by Bork, with a 4%, 14% and 12% dissimilarity to human fetal heart selenium-binding protein, mouse liver selenium binding protein, and mouse liver acetaminophen-binding protein, the function of the SEQ ID NO:1 polypeptide could not be predicted, based on sequence similarity with human fetal heart selenium-binding protein, mouse liver selenium binding protein, and mouse liver acetaminophen-binding protein, nor would it be expected to be the same as that of human fetal heart selenium-binding protein, mouse liver selenium binding protein, and mouse liver acetaminophen-binding protein. Further, even if the polypeptide of SEQ ID NO: 1 are human fetal heart selenium-binding protein, mouse liver selenium binding protein, or mouse liver acetaminophen-binding protein -like proteins, neither the specification nor any art of record teaches what the polypeptide is, what it does. They do not teach a relationship to any specific disease or establish any involvement of the polypeptide in the etiology of any specific disease.

The specification essentially gives an invitation to experiment wherein the artisan is invited to elaborate a functional use for the disclosed polypeptide. Because the claimed invention is not supported by a specific and/or well established utility for the reasons set forth, credibility of any utility cannot be assessed.

35 U.S.C. 112, 1st paragraph (Issue 2)

Claims 1,2,13, and 14 are rejected under 35 U.S.C. 112, 1st paragraph. This rejection is set forth below.

Claims 1-2 and 13-14 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific asserted utility or a well established utility, one skilled in the art clearly would not know how to use the claimed invention.

35 U.S.C. 112, 1st paragraph (Issue 3)

1. Claims 1-2 and 13-14 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The written description in this case only sets forth SEQ ID NO:1 and therefore the written description is not commensurate in scope with the claims drawn to a naturally occurring amino acid sequence having at least 96% sequence identity to SEQ ID NO:1, biologically active fragments of SEQ ID No:1 or immunogenic fragments of SEQ ID No:1.

Claims 1-2 and 13-14 are drawn to a naturally occurring amino acid sequence having at least 96% sequence identity to SEQ ID NO:1, biologically active fragments of SEQ ID No:1 or immunogenic fragments of SEQ ID No:1.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (*See Vas-Cath* at page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 115).

Reiger et al (Glossary of Genetics and Cytogenetics, Classical and Molecular, 4th Ed., Springer-Verlay, Berlin, 1976) clearly define alleles as one of two or more alternative forms of a gene occupying the same locus on a particular chromosome..... and differing from other alleles of that locus at one or more mutational sites (page 17). Thus, the structure of naturally occurring allelic sequences are not defined. With the exception of SEQ ID NO:1, the skilled artisan cannot envision the detailed structure of the encompassed polynucleotides, or the polypeptides encoded thereby. Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The nucleic acid and/or protein itself is/are required. See *Fiers v. Revel*, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Lts.*, 18 USPQ2d 1016.

Furthermore, In *The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

Support for naturally occurring amino acid sequence having at least 96% identity with SEQ ID NO:1, which reads on allelic variants is provided in the specification on page 13, lines 7-8 , where it is disclosed that the invention encompasses HSEBP variants, at at least about 80%, 90% and 95% amino acid sequence identity with the amino acid sequence of HSEBP. Allelic sequence would be expected to encode polypeptide allelic variants. However, no disclosure, beyond the mere mention of allelic variants, and thus the variant polypeptides encoded thereby, is made in the specification. This is insufficient to support the generic claims as provided by the Interim Written Description Guildlines published in the June 15, 1998 Federal Register at Volume 63, Number 114, pages 32639-32645.

The instant specification fails to provide sufficient descriptive information, such as definitive structural or functional features of the claimed genus of polypeptides. There is

no description of the conserved regions which are critical to the structure and function of the genus claimed. There is no description, however, of the sites at which variability may be tolerated and there is no information regarding the relation of structure to function. Structural features that could distinguish the compounds in the genus from others excluded are missing from the disclosure. Furthermore, the prior art does not provide compensatory structural or correlative teachings sufficient to enable one of skill to isolate and identify the polypeptides encompassed and no identifying characteristic or property of the instant polypeptides is provided such that one of skill would be able to predictably identify the encompassed molecules as being identical to those instantly claimed.

Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, the disclosure of specific nucleotide sequences and the ability to screen, is insufficient to describe the genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe and enable the genus as broadly claimed.

Therefore only SEQ ID NO: 1, but not the full breadth of the claims meets the written description provision of 35 USC 112, first paragraph.

(11) Response to Argument

Issues 1 and 2

At p. 5 and 6, of the Brief, Appellant characterizes the invention as a polypeptide sequence encoded by a gene that is expressed in human tissues and that codes for a

polypeptide which is a member of the class of selenium binding proteins having biological functions including forming acting as an arylation target of acetominophen. Based on this, Appellant urges that the claimed invention has numerous practical, beneficial uses in toxicology testing, drug development and diagnosis of disease, none of which requires knowledge of how the polypeptide actually functions. Appellant states that the claimed invention already enjoys significant commercial success. This has been fully considered but is not found to be persuasive for several reasons. The specification does not disclose that the claimed polypeptide is a marker for any specific disease. Absent a disclosure of altered levels or forms of thepolypeptide in diseased tissue as compared with the corresponding healthy tissue, the polypeptide is not a disease marker or an appropriate target for drug discovery or toxicology testing. Finally, evidence of commercial success, while sometimes persuasive as secondary evidence of non-obviousness, is immaterial to utility and enablement. Many products have enjoyed commercial success due to fads or clever advertising, wherein the products would not have met the legal standards for utility and enablement.

Beginning at p. 6, third paragraph, Appellant discusses the Furness declaration submitted. Appellant characterizes the Furness declaration as describing some of the practical uses of the claimed invention in gene and protein expression monitoring applications, thus allegedly demonstrating the examiner's position to be without merit. In particular, Appellant states that the Furness declaration describes how the claimed expressed polypeptide can be used in protein expression monitoring systems that were well-known at the time of the invention, and how those applications are useful in

developing drugs and monitoring their activity. In particular, Appellant states that the Furness declaration describes the use of 2-D PAGE gels and western blotting techniques to monitor protein expression, and further states that the asserted utilities can be used for protein expression analysis on proposed or actual drugs for treating diseases associated with selenium-binding proteins. This is not found to be persuasive. Any new polypeptide can be used in a 2-D PAGE gel or western blot, and thus this asserted utility is not specific. Also, the disclosure that selenium-binding proteins are structurally related to HSEBP does render the asserted utility specific, since the specification does not establish that selenium binding proteins are expressed in any diseased tissues in any way that is different from the way it is expressed in healthy forms of the same tissues. Thus, it is not a target for drug development, toxicology studies, or disease diagnosis. Significant further research would have to be conducted to identify diseases states which correlate with altered levels or forms of the claimed polypeptide. Therefore, this asserted utility is also not substantial.

Beginning at the bottom of p. 5 of the Brief, Appellant criticizes the examiner's position that the claimed polypeptide cannot be useful without precise knowledge of its biological function. However, Appellant is mischaracterizing the examiner's position. A specification can meet the legal requirements of utility and enablement for a new polypeptide as long as the specification discloses a credible, specific and substantial asserted utility for the new polypeptide, or a well-established utility for the claimed polypeptide. A hypothetical example may serve to clarify. For example, a hypothetical specification discloses that a claimed polypeptide is expressed in colon cancer and not

expressed in healthy colon tissue. The hypothetical specification does not disclose the biological activity of the polypeptide. The claimed polypeptide in the hypothetical example would not be rejected under 35 U.S.C. §§ 101 and 112, first paragraph, as it has utility and is enabled as a colon cancer marker. However, such is not the fact pattern here. The instant specification discloses that the claimed polypeptide are structurally related to selenium binding proteins and hypothesizes that the claimed polypeptides are involved in growth control and protection from carcinogenesis, but the expression of the polypeptide in diseased tissues and the corresponding healthy tissues was not evaluated. Therefore, there is no disclosure that the claimed polypeptide are expressed at altered levels or forms in any specific, diseased tissue. It is noted that the instant application was filed 24, April 2001. No evidence has been brought forth during the prosecution history regarding the expression levels in diseased or healthy tissue. Also, no evidence has been brought forth that the claimed polypeptides having specific selenium binding activities.

I. The applicable legal standard

Beginning at p. 7 of the Brief, Appellants summarize case law on the utility requirement. The essential disagreement appears to be the interpretation of what constitutes a specific, substantial and credible utility, as will be explained more fully below.

II. Uses of the claimed polypeptide for the diagnosis of conditions and disorders characterized by expression of HSEBP, for toxicology testing, and for drug development are sufficient utilities under 35 USC§§ 101 and 112, 1st paragraph.

A. The similarities of the claimed polypeptide to another undisputed utility demonstrates utility:

Appellants argue at pages 9-10 that because there is a substantial likelihood that the claimed polypeptide, HSEBP, is functionally related to the selenium binding protein family, that there must also exist a functionally equivalent utility for the claimed polypeptide. This is not found to be persuasive. The difference between the claimed polypeptide and its closest alleged homologues is 4, 12, and 14%. Such a difference in sequence homology could clearly alter the protein structure of the claimed polypeptide giving rise to a entirely new protein with different and distinct functional properties, as outlined by Bowie *et al.* Therefore, the utilities that could have been applied to the other selenium binding proteins may not necessarily apply to those of the instantly claimed polypeptide. Therefore, the claimed utilities applied to the claimed polypeptide are not credible.

B. The uses of HSEBP for toxicology testing, drug discovery, and disease diagnosis are alleged as practical uses that confer specific benefits to the public:

Appellants argue at pages 10-11 of the Brief that the use of HSEBP for toxicology testing, drug discovery, and disease diagnosis are practical uses that confer specific benefits to the public. Appellant states that there is no dispute that the claimed invention is a useful tool in 2-D PAGE analysis or in western blots used to perform

protein expression analysis and to assess drug toxicity. Appellant asserts that such is sufficient to establish utility for the claimed polypeptide. This is not found to be persuasive. While the examiner agrees that any polypeptide, including the claimed polypeptide, can be used in 2-D PAGE gels or western blots, such does not confer patentable utility on the claimed polypeptide. Since any polypeptide can be used in 2-D PAGE gels or in western blots, such a use is not specific to the claimed polypeptide. Just as any orphan receptor can be used in an assay to screen for ligands, such does not confer patentable utility on a particular orphan receptor. Such can be done with any orphan receptor, and thus the asserted utility is not specific. Furthermore, since the specification does not disclose a correlation between any disease or disorder and an altered level or form of the claimed polypeptide, the results of protein expression monitoring assays would be meaningless without significant further research. Therefore, the asserted utility is also not substantial.

Appellant refers to the Furness declaration as explaining the many reasons why a person skilled in the art reading the instant application would have understood that application to disclose the claimed polypeptide to be useful for a number of protein expression monitoring applications, such as in the assessment of drug development or toxicology testing. The Furness declaration discusses 2-D PAGE analysis and western blot analysis for measuring such. Specifically, Appellant quotes from the Furness declaration that a person skilled in the art would have been able to use the claimed polypeptide in protein expression monitoring to develop new drugs for the treatment of diseases associated with selenium binding activity. This is not found to be persuasive.

The instant specification does not substantiate a link between the claimed polypeptide and any disorder. The specification merely discloses that the claimed polypeptide is structurally related to the selenium binding family, and that they are expected to be involved in cell growth regulation and protection from carcinogenesis. The specification does not disclose the results of the required control in order to draw any conclusions regarding disease, namely, that the claimed polypeptide is not expressed (or is expressed at an altered level or form) in the corresponding healthy tissues. Many genes expressed in diseased tissues have nothing whatsoever to do with the disease and are not targets for drug development or toxicology. For example, actin and histone genes are expressed in diseased tissues; they are constitutively expressed in all tissues. These are not suitable targets for drug development or toxicology studies, since disruption of these genes would kill the patient.

Beginning at the 3rd full paragraph of p. 10 of the Brief, Appellant refers to the opinion of Dr. Furness that a person skilled in the art at the time of the invention would have concluded that a 2-D PAGE gels could generate maps for comparison of cells treated with a potential drug candidate with that cell untreated with a drug and that this would prove to be useful in determine the state of cells. Again, this is not found to be persuasive, because the instant specification has not established that the claimed polypeptides are expressed at altered levels or forms in diseased tissue as compared with the corresponding healthy tissue. If the expression of the claimed polypeptide was decreased following the addition of a drug candidate, what would that mean to the skilled artisan? Is it a potential drug, or would administering the compound be likely to

acerbate the disease? If it had been disclosed that the claimed polypeptide is expressed at a higher level in a particular cell proliferative diseased tissue as compared with the corresponding healthy tissue, then the skilled artisan would know that a compound that decreased expression of the polypepetide is a potential drug. However, that is not disclosed by the instant specification. The claimed polypeptides may very well be expressed at equivalent levels in healthy tissues. If that is the case, then the compound would not be a good potential drug. The claimed polypeptides may also very well be expressed at a lower level in a particular diseased tissue as compared to the corresponding healthy tissue. Then a compound that decreased expression of the claimed polypeptide would *not* be a good potential drug. Evidence of a differential expression might serve as a basis for use of the claimed polypeptide as a diagnostic for a disease. However, in the absence of any disclosed relationship between the claimed polypeptide and any disease or disorder, any information obtained from an expression profile would only serve as the basis for further research on the observation itself. "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." *Brenner v. Manson*, 148 USPQ at 696. The disclosure does not present a substantial utility that would support the requirement of 35 U.S.C. §101.

Appellant argues that there can be no reasonable dispute that persons skilled in the art have numerous uses for information about relative protein expression including understanding the effects of a potential drug for treating cell growth disorders and cancers. Again, this is not found to be persuasive, because the specification does not

disclose that the claimed polypeptide is expressed at an altered level or form in any particular disease or disorder as compared to the corresponding healthy tissues.

Appellant refers to other publications that discuss 2-D PAGE analysis with respect to drug screening and toxicology testing at pp. 11 of the Brief. Again, this is not found to be persuasive, because the arguments and evidence merely show that 2-D page analysis technology is important and useful to the scientific community. These publications do not show that the claimed invention has a patentable utility. The use of the claimed uncharacterized polypeptide in such studies would have provided no more information than the use of any other polypeptide. The asserted utility for the claimed polypeptide is not specific to the claimed polypeptide. Due to the lack of disclosure of a correlation between the claimed polypeptide and a particular disorder, the asserted utility is also not substantial, as discussed above.

C. The use of proteins expressed by humans as tools for toxicology testing, drug discovery, and the diagnosis of disease is alleged as "well-established":

Beginning at p. 12 of the Brief, Appellant argues that the claimed polypeptides are useful as tools for toxicology testing, drug discovery, and the diagnosis of disease and that these uses are "well-established". Each of these uses will be addressed individually, because the facts and issues directed to each use are distinct and separable. First, Appellant argues that toxicology testing is a well-established utility and concludes that the claimed polypeptides could be used in this manner and that the claimed invention possesses utility. However, for a utility to be "well-established" it must

be specific, substantial and credible. In this case, genes and polypeptides encoded by the genes are in some combination useful in toxicology testing. However, the particulars of toxicology testing with the claimed polypeptides are not disclosed in the instant specification. Neither the toxic substances nor the susceptible organ systems are identified. Therefore, this is a utility which would apply to virtually every member of a general class of materials, such as any collection of proteins or DNA, but is only potential with respect to the claimed polypeptides. Because of this, such a utility is not specific and does not constitute a "well-established" utility. Further, because any potential diagnostic utility is not yet known and has not yet been disclosed, the utility is not substantial because it is not currently available in practical form. Again, this is a utility which would apply to virtually ever member of a general class of materials, such as any collection of proteins. Even if the expression of Appellant's individual polypeptide are affected by a test compound in an analysis for drug screening, the specification does not disclose any specific and substantial interpretation for the result, and none is known in the art. Given this consideration, the individually claimed polypeptide has no "well-established" use. The artisan is required to perform further experimentation on the claimed material itself in order to determine to what "use" any expression information regarding this polypeptide could be put.

With regard to drug discovery and development, Appellant mentions expression profiling as one use of the claimed polypeptide. Appellant refers to recent developments as providing evidence that the benefits of this information are already beginning to manifest themselves. However, Appellant is incorrect in asserting that the

efficacy (ability of producing a desired effect) of a compound could be evaluated from the result of a transcript image because there is no way to assess the meaning of any individual hit obtained from this procedure. The first requirement is that one must know the biological significance of the polypeptides(s) which is(are) being evaluated. Without this information, the results of the transcript image are useless because one would not know if the polypeptide expressed should be increased or decreased or even what significance could be attributed to such changes in expression profiles.

With regard to diagnosis of disease, in order for a polypeptide to be useful, as asserted, for diagnosis of a disease, there must be a well-established or disclosed correlation or relationship between the claimed polypeptide and a disease or disorder. The presence of a polypeptide in tissue that is derived from cancer cells is not sufficient for establishing a utility in diagnosis of disease in the absence of some information regarding a correlative or causal relationship between the expression of the claimed polypeptide and the disease. If a molecule is to be used as a surrogate for a disease state, some disease state must be identified in some way with the molecule. There must be some expression pattern that would allow the claimed polypeptide to be used in a diagnostic manner. Many proteins are expressed in normal tissues and diseased tissues. Therefore, one needs to know, e.g., that the claimed polypeptide is either present only in cancer tissue to the exclusion of normal tissue or is expressed in higher levels in diseased tissue compared to normal tissue (i.e. overexpression). Evidence of a differential expression might serve as a basis for use of the claimed polypeptide as diagnostics for diseases. However, in the absence of any disclosed relationship

between the claimed polypeptide or the proteins that are encoded thereby and any disease or disorder and the lack of any correlation between the claimed polypeptide with any known disease or disorder, any information obtained from an expression profile would only serve as the basis for further research on the observation itself. "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." *Brenner v. Manson*, 148 USPQ at 696. The disclosure does not present a substantial utility that would support the requirement of 35 U.S.C. §101.

D. Objective evidence is alleged to corroborate the utilities of the claimed invention

Beginning at p. 13 of the Brief, Appellant argues that a "real-world" utility exists if actual use or commercial success can be shown. Citing case law, Appellant urges that such a showing is conclusive proof of utility. Appellant argues that a vibrant market has developed for databases containing all expressed genes including polypeptides expressed from those genes, including those of Incyte, the real party at interest in the instant appeal. Appellant urges that Incyte's customers and the scientific community have acknowledged that Incyte's databases have proven valuable, and that the databases including the claimed polypeptides would be even more valuable. Appellant's arguments have been fully considered but are not deemed to be persuasive. The case law indicates that a rejection under 35 U.S.C. § 101 *for lack of operability* can be overcome by a showing of actual use or commercial success. The instant issue is whether or not the asserted utilities meet the three-pronged test for credibility,

specificity, and substantiality. Such is not necessarily addressed by a showing of commercial success or actual use. As argued previously, many products which lack patentable utility enjoy commercial success, are actually used, and are considered valuable. These include silly fads such as pet rocks, but also include serious scientific products like orphan receptors.

III. The patent examiner's rejections are alleged as being without merit

A. The precise biological role or function of an expressed polypeptide is alleged as being not required to demonstrate utility

Beginning at p. 14 of the Brief, Appellant characterizes the examiner's rejection as being based on the grounds that, without information as to the precise biological role of the claimed invention, the claimed invention lacks specific patentable utility. Appellant characterizes the examiner's position as it is not enough that a person skilled in the art could use and would want to use the claimed invention either by itself or in a 2-D PAGE gel or western blot, but that Appellant also is required to provide a specific and substantial interpretation of the results generated in a given expression analysis. Appellant argues that specific and substantial interpretations regarding biological function may be required by technical journals, but are not necessary for patents. Appellant urges that the relevant question is not how or why the invention works, but whether the invention provides an identifiable benefit. Appellant argues that the present invention meets this test. Appellant argues that the threshold for patentable utility is low. Appellant urges that only throwaway utilities are insufficient, and that knowledge of biological function is not required. This is not found to be persuasive, as it

mischaracterizes the examiner's position. The rejection never states that the precise biological role of a polypeptide is required for it to possess patentable utility. If a polypeptide is disclosed as being differentially expressed in a disease or disorder, even if nothing is known or hypothesized about the activities of polypeptide, then the polypeptide has patentable utility as a disease marker and in the toxicology/drug screening 2-D PAGE gel assays discussed at length by Appellant. However, if a specification does not disclose such information, as is the case here, then there is no patentable utility. If a compound causes the claimed polypeptide to be expressed at a decreased level in a 2-D PAGE gel or western blot, does that mean the compound is a potential drug or a potential toxin? That determination requires significant further research, and thus the asserted utility is not substantial. Also, any expressed polypeptide *can* be used in a 2-D PAGE gel or western blot; thus the unasserted utility is also not specific.

B. Membership in a class of useful products can be proof of utility

Beginning at p. 15 of the Brief, Appellant asserts that the examiner improperly refused to impute the utility of selenium-binding family to the claimed invention. Appellant urges that the case law requires only that the class not contain a substantial number of useless members. Appellant urges that the examiner has treated HSEBP as if they were in the general class of all polypeptides, rather than the selenium-binding family. Appellant concludes that the examiner has not presented any evidence that the selenium binding homologue class of proteins has any, let alone a substantial number, of useless members. This is not found to be persuasive. The selenium binding family is

functionally highly diverse, as evidenced by the references made of record in the rejection. When there is great functional diversity in a structurally related class of compounds, the class cannot be used to predict a utility for a new compound that fits in the class by structural similarity. Such is the case here.

Appellant argues that the selenium-binding protein family is known to be a target for the arylation of acetominophen, and the person of ordinary skill in the art need not know anything more about the claimed invention in order to be able to use it. Appellant urges that knowledge that HSEBP is a selenium-binding homolog is more than sufficient to make the useful for the diagnosis and treatment of selenium-binding disorders. Appellant concludes that these facts must be accepted as true in the absence of evidence or sound scientific reasoning to the contrary. This is also not found to be persuasive. There is a great diversity of cell types affected by these polypeptides. The specification does not disclose which cell types are responsive to the polypeptides encoded by the claimed polypeptides. Significant further research would be required of the skilled artisan to determine which cells are responsive, and thus the asserted utility is not substantial. Similarly, mere expression in a cancer cell does not mean that the polypeptide is an appropriate target for drug development or toxicology testing. Cancer cells express many polypeptides, such as constitutively expressed proteins, which are not appropriate targets. The specification has not disclosed a specific disease or disorder of any type wherein the claimed polypeptide is expressed at altered amounts or forms relative to the required control healthy tissue. Significant further research would

be required of the skilled artisan to identify such a disease or disorder. Therefore the asserted utility is not substantial.

C. Because the uses of HSEBP in toxicology testing, drug discovery, and disease diagnosis are asserted as practical uses beyond mere study of the invention itself, the claimed invention is alleged to have utility.

At p. 16 of the Brief, Appellant argues that the rejection is incorrectly based on the grounds that the use of an invention as a tool for research is not a substantial use. Appellant urges that only a limited subset of research uses are not substantial: those in which the only known use for the claimed invention is to be an object of further study, thus merely inviting further research. This is not found to be persuasive. As discussed above, whereas a scale or a microarray or a gas chromatograph has patentable utility as a research tool, the objects being evaluated with those research tools do not necessarily have patentable utility. In the instant case, the claimed polypeptide is not disclosed as having a specific activity, or having any property (such as a differential pattern of expression in diseased tissue) that can be specifically useful. The claimed invention is, in fact, the object of further study, merely inviting further research. None of the utilities asserted for the claimed polypeptide meets the three-pronged test of being specific, substantial and credible.

D. The patent examiner is alleged to have failed to demonstrate that a person skilled in the art would reasonably doubt the utility of the claimed invention.

Beginning at the top of p. 17 of the Brief, Appellant argues that, identification of the articular function of what is claimed is not needed to fulfill the utility requirement of the law. This is not found to be persuasive, because the specification has not asserted any utility for the claimed polypeptide that is credible, specific and substantial, regardless of whether or not the asserted utility is based on the encoded polypeptide's function. As stated earlier, if the specification had provided a specific, substantial and credible assertion of utility for the claimed polypeptide unrelated to the function of the encoded polypeptides, such would have been accepted, and not rejection under 35 U.S.C. § 101 would have been made. For example, if the claimed polypeptide had been disclosed as mapping to a chromosomal location associated with a specific genetic disorder, and the specification asserted that the claimed polypeptide could have been used as a diagnostic probe related to the disease, such would have been accepted as a patentable utility even though it is unrelated to the function of the polypeptides.

Appellant also criticizes the rejection's use of Bork (2000, Genome Research 10:398-400), Burgess *et al* (J. Cell Biol. 1990;111:2129-2138), Lazar *et al* (Mol. Cell. Biol., 1988;8:1247-1252) and Bowie et al. (1990, Science 247:1306-1310). Specifically, Appellant urges that the teachings of Bowie et al. are counter to the outstanding rejections and supportive of the asserted utilities for NDB17. Appellant characterizes Bowie et al. as being directed to studying the effects of site-directed mutagenesis to determine the relative importance of these residues to protein structure and function, which Appellant urges is not relevant to the instant invention. Appellant argues that

Bowie et al. support Appellant's use of amino acid sequence homology to reasonably predict the utility of the polypeptide, since Bowie et al. teach that evaluating sets of related sequences, which are members of the same gene family is an accepted method of identifying functionally important residues that have been conserved in evolution. Appellant submits that the amino acid differences among the polypeptides encoded by the claimed polynucleotides and known growth factor proteins are likely to occur at positions of minimal functional importance. Appellant concludes that one of ordinary skill in the art would view the level of conservation between the claimed polypeptide encoding NADH dehydrogenase subunits is indicative of a common function. This has been fully considered but is not found to be persuasive. The proteins discussed by Bowie et al. include globins, cytochromes and λ repressors, all of which are well conserved structurally *and functionally.* While there are many families of polypeptides which are conserved both structurally and functionally, including most enzymes and "housekeeping" polypeptides such as actins and histones, the art recognizes that structural similarity among growth factors and hormones is not predictive of functional similarity. Also, the proteins discussed by Bowie et al. were already known to have a particular activity. Such is not the case here. The specification discloses the sequences of the claimed polypeptides, but the functions of the encoded polypeptides are not disclosed. Bowie et al. was cited to establish that, while it should be possible to predict tertiary structure from sequence, and subsequently to infer detailed aspects of function from the structure, both problems are considered in the art to be extremely

complex. Bowie et al. states plainly that it seems unlikely that either problem will be solved in an exact manner in the near future (p. 1306, left hand column).

At the bottom of p. 17 of the Brief, Appellant characterizes Brenner et al. (1998, PNAS USA 95:6073-6078) as showing that 30% identity is a reliable threshold for establishing evolutionary homology between two sequences aligned over 150 residues. Appellant points to the specification as disclosing that HSEBP is more than 96,88, and 88% identical to other selenium binding protein. Appellant concludes that one of ordinary skill in the art would expect HSEBP to possess the evolutionarily conserved structural and functional characteristics of selenium binding proteins. This is not found to be persuasive. The rejection never states that HSEBP is unrelated to selenium binding protein. They are clearly structurally related. However, the rejection sets forth that, *among related polypeptides* in the selenium-binding families, structural similarity is not predictive of functional similarity.

Appellant concludes this section by arguing that the cited evidence is insufficient to support the rejections of the claims. Appellant urges that the only relevant evidence of record shows that a person of ordinary skill in the art would not doubt that the claimed polypeptides encode selenium-binding homologs, which are known to have specific utility. Appellant argues that, by ignoring the reasonable correlation requirement of the case law, the rejection is not a *prima facie* case, and the rejection does not shift the burden to Appellant for rebuttal. This has been fully considered, but has not been found persuasive. The assertion that the disclosed NDB17 has biological activities similar to known selenium binding family is not credible in the absence of supporting evidence,

because the relevant literature reports numerous examples of polypeptide families wherein individual members have distinct, and even opposite, biological activities and that the substitution of amino acids into the known proteins can alter the structure and ultimately effect the function.

IV. By requiring the patent applicant to assert a particular or unique utility, it is alleged that the patent examination utility guidelines and training materials applied by the patent examiner misstate the law.

Beginning at p. 27 of the Brief, Appellant challenges the legality of the Patent Examination Utility Guidelines. Since a Primary Examiner has no authority to comment on the legality of the Guidelines, this issue will be reserved for ruling by the Board of Patent Appeals and Interferences.

V. To the extent the rejection of the invention under 35 U.S.C. § 112, first paragraph, is based on the alleged improper rejection for lack of utility under 35 U.S.C. § 101, it is alleged that the rejection must be reversed

As Appellant indicates at p. 29 of the Response, a rejection under § 112, first paragraph, may be affirmed on the same basis as a lack of utility rejection under § 101. *See, e.g., In re Swartz*, 56 USPQ2d 1703 (Fed. Cir. 2000); *In re Kirk*, 153 USPQ 48 (CCPA 1967).

Therefore, for reasons set forth above, Appellants arguments and exhibits have been fully and carefully considered, but are not considered sufficient to rebut the prima facie case of lack of utility and it is believed that the rejections should be sustained.

Issue 3

At page 29, appellants argue that the Examiner has ignored the disclosure regarding the claimed polypeptide fragments and variants. However, this argument has been fully considered but is not deemed persuasive because appellants have described only a single naturally occurring sequence, that of SEQ ID NO: 1. No other naturally occurring sequences have been described as obtainable from human, nor any other animal. A breadth of 96% identity at the protein level would reasonably be expected to encompass homologues obtained from other primate species such as macaque, rhesus, gibbon, as well as from non-primate species, such as rat or mouse, giraffe, hippo, or even frog or yeast, depending upon the evolutionary conservation of the gene in question. Appellants have provided no information or description about how conserved the protein in question is, that is, how similar the homologues from other species would be expected to be, nor have they described a single species other than the single allele (instance) of the gene as obtained from a single human. There is no description about the function of the gene nor the protein encoded thereby, such as would allow one of skill in the art to predict what portions of the disclosed sequence would be expected to be conserved. Accordingly, the mere recitation of "naturally occurring" does not obviate the issue raised with respect to written description. Similarly, with respect to claims to proteins with 96% identity, again, no such naturally occurring variants have been disclosed, nor has any function been described for the encoded protein, nor ways in which the encoded protein might be altered while retaining that function. With further respect to this issue, it is a polypeptide that is being claimed;

without having a written description of all naturally occurring sequences within the metes and bounds of the claims, one would not be capable of determining whether or not a given species was claimed.

At page 31, appellants argue that variants are described, for example, at pages 6 and 13 of the specification. This argument has been fully considered but is not deemed persuasive. Page 6 of the specification merely defines what an allelic variant *is*. It does not describe even a single naturally occurring allelic variant. Similarly, at pages 13, the specification merely describes some of the things that *may* happen to be a variant. However, it is not true that one could find any and all possible changes within a given gene, and the specification has described not a single variant of SEQ ID NO: 1. Further, even *if* the specification had described some naturally occurring human allelic variants within the scope of the claims, such would not be commensurate in scope with the claims. This is because one of ordinary skill in the art would 4% at the protein level to read on species homologues, that is, similar sequences as isolated from different biological species. There is not a single sequence disclosed that is obtained from another biological species.

Appellants argue that one of ordinary skill in the art would recognized naturally occurring variants of SEQ ID NO: 1 having 96% identity to SEQ ID NO: 1; this is not true. One could certainly determine whether a protein that one had obtained from nature were 96% identical to SEQ ID NO: 1, but that same person, handed a protein in a test tube, would have no way of determining whether that protein were 'naturally occurring'.

Appellants argue that the claims "do not define a genus which is "highly variant"". Applicants argue that the Brenner reference states that 30% identity is a reliable threshold for establishing evolutionary homology between two sequences aligned over at least 150 residues, and that the present invention is directed to polypeptides related to the amino acid sequence of SEQ ID NO: 1. Brenner et al. assess that 40% identity over at least 70 residues is reliable in signifying homology between proteins. Based on these evolutionary calculations, Applicants continue to assert that the variation of the instant 96% variants of instant SEQ ID NO:1 is far less than what Brenner et al. had envisioned for related proteins. These arguments have not been found to be persuasive, because Brenner's calculations represent theoretical assessments and can form the basis of a hypothesis, however these calculations while providing evolutionary information do not establish the relationship of a protein biologically without a second criterion such as function, or location, or occurrence, or associated expression. Therefore, in the instant case, Brenner's calculations and applicants' analogy are well accepted as two distinct facts, but do not apply to the current grounds of rejection of lack of written description of the claimed genus described only by the chemical structure of one member without a description of how that structure correlates with the definitive properties of the genus encompassed.

To elucidate further, appellant is misdirecting the issue. The issue here is not whether or not sequences 96% identical to SEQ ID NO: 1 would be considered to be evolutionarily related to such, but whether or not the specification as originally filed provides an adequate written description of the 'genus'. While 96% identity is certainly sufficient to establish that two proteins are structurally similar and/or evolutionarily related, it is not predictive of function. Evolutionary relatedness merely means that two entities (proteins, nucleic acid sequences, or even whole organisms) are evolutionary descendants of a common ancestor. In the process of diverging, said proteins, nucleic acids or organisms take on different structures and functions. To follow appellant's argument to the level of organisms, it would appear that appellants would urge that the written description of a monkey constitutes an adequate written description of a human, as the two are well known to be over 96% identical. At the protein level, there are less extreme examples; VEGF (a member of the PDGF, or platelet-derived growth factor, family) is mitogenic for vascular endothelial cells but not for vascular smooth muscle cells, which is opposite to the mitogenic activity of naturally occurring PDGF which is mitogenic for vascular smooth muscle cells but not for vascular endothelial cells, though the two are closely related. The specification as originally filed does not define a common structure or function that defines the genus claimed, and the written description is not commensurate in scope to all possible naturally occurring sequences at least 96% identical to such, which would be expected to encompass evolutionarily related, but structurally and functionally distinct, genes and proteins.

Bridging pages 35-36, appellant argues that the art has matured considerably since the *Lilly* and *Fiers* cases. While this is true, it is not of consequence as regards this rejection for lack of adequate written description of the claimed genus. The key issue here is that appellants have disclosed a single polypeptide sequence. No function has been attributed to the polypeptide. The claims encompass all naturally occurring amino acid sequences that are at least 96% identical to SEQ ID NO: 1. No defining characteristics have been disclosed to identify the critical features of the genus, and no species homologues or allelic variants have been described or disclosed. Further, appellant's own arguments of evolutionary relatedness would suggest that appellant would urge that the disclosure of a single naturally occurring sequence is sufficient written description to entitle appellant to claim the breadth of yet-undiscovered evolutionarily related but structurally and functionally distinct nucleic acids.

Therefore, for reasons set forth above, Appellants arguments and exhibits have been fully and carefully considered, but are not considered sufficient to rebut the prima facie case of lack of utility and it is believed that the rejections should be sustained.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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